DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

3162 '99 NOV -4 P1:38

NOV 2 1999

T.S. Elliott, Ph.D., MPH
The Procter & Gamble Company
11511 Reed Hartman Highway
Cincinnati, Ohio 45241

Re: Docket No. 78N-0038
Comment No. C555 and CP8

Dear Dr. Elliott:

This letter is in response to your letter dated May 11, 1999, and filed as Comment No. C555 under Docket No. 78N-0038 in the Dockets Management Branch. Your comment was submitted in response to David J. Horowitz's letter dated April 8, 1999, requesting appropriate in vivo ultraviolet A (UVA) efficacy data to demonstrate the UVA radiation protection potential of avobenzone with phenylbenzimidazole sulfonic acid and avobenzone with zinc oxide. Your comment provided efficacy data using the in vivo UVA protection factor (PFA) methodology to support the "broad spectrum" and/or UVA radiation protection potential of these combinations. Based on this information, you urged the agency to approve your citizen petition (CP8) and amend the monograph for over-the-counter (OTC) sunscreen drug products to include these combinations.

The Division of OTC Drug Products has reviewed the additional data you have submitted concerning the efficacy of these combinations and determined that the data are sufficient to demonstrate the "broad spectrum" and/or UVA radiation protection potential of avobenzone with phenylbenzimidazole sulfonic acid and avobenzone with zinc oxide. The following specific comments concern the information submitted.

Your submission contained a final clinical study report for the static PFA determination of the following five sunscreen formulations:

1) A - 1.5 percent phenylbenzimidazole sulfonic acid
2) C - 3 percent avobenzone
3) K - 1.5 percent phenylbenzimidazole sulfonic acid with 3 percent avobenzone
4) Q - 4 percent zinc oxide
5) R - 4 percent zinc oxide with 3 percent avobenzone

78N-0038

LET169

A single double blind study was conducted using the PFA methodology as described by Johnson & Johnson Consumer Products (Ref. 1). The PFA test is a modification of the sun protection factor (SPF) test proposed in the advance notice of proposed rulemaking for OTC Sunscreen Drug Products (43 FR 38206 at 38265 to 38266). For the PFA test method, the light source is modified to emit only UVA radiation. The biological endpoint used is a change in skin color, either erythema (redness) or tanning (browning) of the skin observed 16 to 24 hours after ultraviolet radiation exposure. The lowest dose of UVA radiation that causes a minimally perceptible response is defined as the minimal response dose (MRD). The MRD is determined for unprotected skin (MRD_u) and for the sunscreen protected skin (MRD_p). The PFA is the ratio of MRD_p divided by the MRD_u.

A total of 39 subjects were enrolled in the study and 38 (25 female and 13 male) completed all study phases. Thirty-three (20 female and 13 male) were Fitzpatrick skin type II and six (all female) were type I. PFA values were determined on at least 20 subjects for each test formulation. No adverse events were reported. Results for each test formulation are shown below:

Test Formulation	Subjects	Mean PFA	Standard Deviation	Standard Error
A	21	1.4	0.3	0.1
C	21	3.1	0.6	0.1
K	21	3.6	0.8	0.2
Q	21	2.3	0.4	0.1
R	20	5.6	1.4	0.3

Labeling

In the tentative final monograph (TFM) for OTC sunscreen drug products, the agency proposed that an OTC sunscreen ingredient must have an absorption spectrum extending to 360 nanometers (nm) or above in order for a product containing that ingredient to display UVA radiation protection claims in its labeling (58 FR 28194 at 28233). The agency also stated that the product would have to demonstrate meaningful UVA radiation protection by satisfying "yet to be established" UVA radiation testing procedures that would be included in the monograph. The agency described suggested interim UVA radiation test procedures in the TFM (58 FR 28248 to 28250) and in a notice of public meeting (59 FR 16042) to discuss such testing procedures.

Although the agency continues to evaluate data and information relative to a monograph method for determining UVA radiation protection (see enclosed copy of January 27, 1999, minutes of

meeting), we find that the submitted study provides sufficient evidence to demonstrate that 3 percent avobenzone with 1.5 percent phenylbenzimidazole sulfonic acid and 3 percent avobenzone with 4 percent zinc oxide were significantly more effective than 1.5 percent phenylbenzimidazole sulfonic acid or 3 percent zinc oxide alone in protecting against UVA radiation. Although phenylbenzimidazole sulfonic acid does not provide significant UVA radiation protection (due to it being primarily a UVB radiation absorbing sunscreen ingredient), we believe that phenylbenzimidazole sulfonic acid when combined with avobenzone can contribute to "broad spectrum" protection. Due to the ability of zinc oxide to provide "broad spectrum" protection, we also believe that zinc oxide combined with avobenzone can contribute to "broad spectrum" protection and provide added protection from UVA radiation. Any sunscreen drug product bearing UVA protection claims requires both SPF and UVA radiation protection testing of the finished product. The agency plans to propose a monograph method for determining UVA radiation protection in a future issue of the FEDERAL REGISTER. Until the agency proposes a monograph UVA radiation testing method, the agency considers testing procedures similar to the method described above (Ref. 1), and the methods described by R. W. Gange et al. (Ref. 2) and N. J. Lowe et al. (Ref. 3) as appropriate for determining the UVA radiation protection potential of a finished OTC sunscreen drug product.

In amendments to the TFM dated September 16, 1996 (61 FR 48645) and October 22, 1998 (63 FR 56584), the agency proposed specific UVA radiation or "broad spectrum" label claims for OTC sunscreen drug products containing avobenzone or zinc oxide, respectively. In the final rule for OTC sunscreen drug products, the agency stated that UVA labeling may continue in accord with the TFM and its amendments until the agency addresses comments pertaining to UVA radiation testing methods and related UVA protection claims in a future issue of the FEDERAL REGISTER (64 FR 27666 at 27672). Accordingly, in addition to applicable labeling in §§ 352.50 through 352.60 of the sunscreen final monograph, the Division of OTC Drug Products intends to propose that sunscreen drug products containing avobenzone with phenylbenzimidazole sulfonic acid and avobenzone with zinc oxide making UVA protection claims be labeled in accord with the September 16, 1996, amendment to the TFM.

Please be advised that marketing of OTC sunscreen drug products with any of the UVA-related claims proposed by the agency are subject to the risk that the agency may adopt a different position in a future issue of the FEDERAL REGISTER. The agency discussed this possibility and its current views relative to UVA test methodologies and labeling at a public meeting on January 27, 1999, and in an October 1, 1999 letter responding to a citizen petition submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) (see enclosures).

Conclusion

In summary, we consider the safety studies discussed in our September 15, 1998, letter to you in conjunction with the efficacy study discussed above sufficient to support the safety and efficacy of avobenzone with phenylbenzimidazole sulfonic acid and avobenzone with zinc oxide when used in the concentrations established for each ingredient in § 352.10 of the final monograph for OTC sunscreen drug products.

Marketing of products containing avobenzone with phenylbenzimidazole sulfonic acid and avobenzone with zinc oxide will not be permitted until: (1) A proposal to amend the sunscreen final monograph is published in the FEDERAL REGISTER setting forth the conditions under which avobenzone in combination with phenylbenzimidazole sulfonic acid and zinc oxide can be included in the sunscreen monograph, (2) the comment period for that proposal has closed, (3) the agency has evaluated all comments to the proposal, and (4) another FEDERAL REGISTER notice is published announcing the agency's determination concerning the marketing of sunscreen drug products containing these combinations.

We intend to recommend that the Associate Commissioner for Regulatory Affairs respond to your petition in the above manner. Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket and the citizen petition number shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. This letter should not be considered a formal ruling on your petition. That occurs when you are sent a response by the Associate Commissioner for Regulatory Affairs.

We hope this information will be helpful.

Sincerely yours,

Charles J. Ganley, MD
Director
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosures: List of References
January 27, 1999, minutes of meeting
October 1, 1999, letter to CTFA

References

(1) Comments No. RPT5, and CR7, Docket No. 78N-0038, Dockets Management Branch.

(2) Gange, R. W. et al., "Efficacy of a Sunscreen Containing Butyl Methoxydibenzoylmethane Against Ultraviolet A Radiation in Photosensitized Subjects," Journal of the American Academy of Dermatology, 15:494-499, 1986.

(3) Lowe, N. J. et al., "Indoor and Outdoor Efficacy Testing of a Broad Spectrum Sunscreen Against Ultraviolet A Radiation in Psoralen-sensitized Subjects," Journal of the American Academy of Dermatology, 17:224-230, 1987.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 78N-0038.

TO: Dockets Management Branch, HFA-305

[X] The attached material should be placed on public display under the above referenced Docket No.

[ ] This material should be cross-referenced to Comment No. 555 & CP8.

Charles J. Ganley, M.D.

Attachment